MedWatch Safety Report

3565931-7-00-01

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

McNeil Consumer Healthcare
McNeil Consumer Healthcare
Fort Washington, PA 19034-2299

Page ____ of ____

Approved by FDA on 11/15/93

Mfr report #

UF/Diet report #

FDA use only

A. Patient information

1. Patient Identifier	2. Age at time of event:	3. Sex	4. Weight
unknown In confidence	62 yrs or ____ Date of birth:	(X) female ( ) male	unk lbs or kgs

B. Adverse event or product problem

1. X Adverse event and/or Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)

( ) death (mo/day/yr)
( ) life-threatening
(X) hospitalization - initial or prolonged
( ) disability
( ) congenital anomaly
(X) required intervention to prevent permanent impairment/damage
(X) other: recovered

3. Date of event: unknown (mo/day/yr)

4. Date of this report: 09/21/00 (mo/day/yr)

5. Describe event or problem

Abstract # 6599 from the 2000 Annual Meeting of the American Gastroenterological Association of fulminant hepatic failure (LIVER FAILURE) caused by the coexistence of APAP, hepatitis C virus & alcohol. According to abstract, a 62 yo AA female w/ a hx of chronic ETOH use (approx 60g/day x 40 yrs) was admitted w/ abd pain, nausea, vomiting, jaundice, & altered mental status after ingesting 1-1.5 g/day of APAP for shoulder pain during the 4 days preceeding admission. On PE, pt had grade III ENCEPHALOPATHY & icterus but no stigmata of chronic liver disease. Initial lab data: arterial pH=7.1, APAP=158.9 ug/ml, tbili=4.7 mg/dl, AST=19621 U/L, ALT=4545 U/L, PT=24.3, Cr=5.7 mg/dl, NH3=161 umol/L, Factor V=21%, Factor VII=17%. Serological profile revealed a (+) HCV antibody test w/a viral load of greater than 1 million. Pt satisfied all poor prognostic criteria of APAP induced-fulminant hepatic failure identified by King's college criteria & other prognostic methods. Pt was tx'd w/NAC within 6 hrs of presentation. Pt's 12-day ICU course was (See Sect B7)

6. Relevant tests/laboratory data, including dates

Initial lab data: arterial pH=7.1, APAP=158.9, tbili=4.7 (peak value 32.4), AST=19621, ALT=4545, PT=24.3, Cr=5.7, NH3=161, Factor V=21% & Factor VII=17%, HCV antibody (EIA-II)=(+) w/ viral load greater than 1 million

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

hx of chronic ETOH use (approx 60 g/day x 40 yrs) (Sect B5 cont) complicated by multi-system organ failure: acute renal failure (KIDNEY FAILURE), PANCREATITIS, ARDS, respiratory failure (APNEA), intravascular coagulopathy (COAGULATION DISORDER), bacterial peritonitis, SEPSIS & rhabdomyolysis (MYOPATHY). With aggressive care, pt's (See Sect C10)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)

#1 unspecified acetaminophen product

#2

2. Dose, frequency & route used

#1 1-1.5 g/day, po

#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)

#1 4 days PTA

#2

4. Diagnosis for use (indication)

#1 shoulder pain

#2

5. Event abated after use stopped or dose reduced

#1 (X) Yes ( ) No ( ) N/A

#2 ( ) Yes ( ) No ( ) N/A

6. Lot # (if known)

#1 Unknown

#2

7. Exp. date (if known)

#1 Unknown

#2

8. Event reappeared after reintroduction

#1 ( ) Yes ( ) No (X) N/A

#2 ( ) Yes ( ) No ( ) N/A

9. NDC # - for product problems only (if known)

- -

10. Concomitant medical products and therapy dates (exclude treatment of event)

unknown (Sect B7 cont) condition gradually improved, despite a dismal prognosis. Three weeks after admission, pt was DC. Pt remains clinically stable & is followed as an outpt. Pt is undergoing alcohol rehab & being considered for HCV tx.

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

McNeil Consumer Healthcare
Medical Affairs
7050 Camp Hill Road
Ft. Washington, PA 19034

2. Phone number: 215-273-7303

3. Report source (check all that apply)

( ) foreign
( ) study
(X) literature
( ) consumer
(X) health professional
( ) user facility
( ) company representative
( ) distributor
( ) other:

4. Date received by manufacturer (mo/day/yr): 09/21/00

5.
(A) NDA # 19-872
IND #
PLA #
pre-1938 ( ) Yes
OTC product (X) Yes

6. If IND, protocol #

7. Type of report (check all that apply)

( ) 5-day (X) 15-day
( ) 10-day ( ) periodic
(X) Initial ( ) follow-up #

8. Adverse event term(s)

LIVER FAILURE
ENCEPHALOPATHY
KIDNEY FAILURE
PANCREATITIS
APNEA
COAGULATION DIS
SEPSIS
MYOPATHY

9. Mfr. report number: 1433451A

E. Initial reporter

1. Name, address & phone #

Vivek Kaul
Albert Einstein Medical Center
5501 Old York Road
Philadelphia, PA 19141

DSS
OCT 0 3 2000

2. Health professional?	3. Occupation	4. Initial reporter also sent report to FDA
(X) Yes ( ) No		( ) Yes ( ) No (X) Unk

FDA Facsimile Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

OCT 0 2 2000

Individual Safety Report

3585931-7-00-02

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DSS
OCT 03 2000

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OCT 03 2000

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Facsimile Form 3500A

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Supplement to

Gastroenterolo

Digestive Disease Week and the 101st Annual Meeting of the American Gastroenterological Association

May 21-24, 2000, San Diego, CA

- Program of the Annual Meeting of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the Gastroenterology Research Group, the Society for Surgery of the Alimentary Tract, and the American Society for Gastrointestinal Endoscopy
- Abstracts of Papers Submitted to the American Gastroenterological Association
- Abstracts of Papers Submitted to the American Association for the Study of Liver Diseases
- Abstracts of Papers Submitted to the Society for Surgery of the Alimentary Tract

6596

DAILY INTERFERON ALPHA 2B AND RIBAVIRIN COMBINATION THERAPY FOR CHRONIC HEPATITIS C PATIENTS WHO HAVE RELAPED OR NOT RESPONDED TO PREVIOUS TREATMENT: ONE YEAR TREATMENT RESULTS.

Zeki Karasu, Ahmet O. Gurakar, Ahmad S. Jazzar, Carolyn Emmett, Greg C. McMillon, Bakr M. Nour, Harlan I. Wright, INTEGRIS Baptist Med Ctr, Zuhdi Transplant Institute, Oklahoma City, OK.

BACKGROUND: Interferon (IFN) alpha 2b and ribavirin combination has increased success rate in the treatment of chronic hepatitis C. The optimal dose, frequency and duration of this combination treatment is not yet clear. Some reports on hepatitis C virus kinetics suggest that daily IFN is more advantageous than TIW administration. We investigated the efficacy of long-term (12 month) daily IFN alpha 2b and Ribavirin combination therapy for chronic hepatitis C patients, who have either relapsed or not responded to previous IFN alpha 2b therapy. METHODS: Between September 1997 and March 1998, 25 noncirrhotic hepatitis C patients with mean age of 44.0 ± 6.9 years were enrolled in an attempt to treat protocol. Thirteen were males and 12 were females. Patients were administered daily 3 MU IFN alpha 2b SQ as well as daily Ribavirin PO at a dose of 1000-1200 mg. Serum samples were drawn weekly for the first month and then on a monthly basis thereafter for liver function tests and complete blood count. Serum HCV-RNA was tested at 12 and 48th week of treatment. Treatment failures were described as HCV-RNA positivity at the end of the 48th week of treatment. RESULTS: Pre-treatment serum HCV-RNA levels were between 50,000 to 5,000,000 copies/mL with a medium of 535,000. Total of 15 (60%) of patients were removed from the protocol because of noncompliance (2), anemia (2), fatigue (3), skin lesions (3), depression (3), bronchospasm (1) and retinal hemorrhage (1). Of the ten patients who completed the study, 7 patients needed dose reduction of Ribavirin mainly due to anemia, severe fatigue and rash. Eight of this group of 10 patients (6 of 6 relapsers and 2 of 4 previous nonresponders) became HCV-RNA negative at the end of the 48th week. Total HCV-RNA clearance was 40% but if we consider only those who could complete the treatment, this rate increases to 80% for the whole group and 100% for the relapsers. CONCLUSION: Although further studies on larger patient populations are necessary, our limited data suggests daily IFN alpha 2b and Ribavirin combination to be highly effective, especially among relapsers. High drop out rate seems to be the most limiting factor for this type of treatment. Also, patients who have not previously responded to IFN 2b can be considered to be a reasonable candidate. Because of the high risk of anemia and fatigue, these individuals require close monitoring. DISCLOSURE: This research was founded in part by a grant from Integrated Theraputics.

6597

DAILY USE OF CONSENSUS INTERFERON FOR CHRONIC HEPATITIS C AMONG PATIENTS WHO HAD RELAPSED OR NOT RESPONDED TO PREVIOUS TREATMENT WITH ALPHA INTERFERON 2B: ONE YEAR TREATMENT RESULTS.

Zeki Karasu, Ahmet O. Gurakar, Ahmad S. Jazzar, Carolyn Emmett, Sandettie Hulagu, Mujdat Balkan, Bakr M. Nour, Harlan I. Wright, INTEGRIS Baptist Med Ctr, Zuhdi Transplant Institute, Oklahoma City, OK.

BACKGROUND: Consensus interferon (CIFN) is a synthetic recombinant Type I interferon which has been recently approved for treatment of hepatitis C on the basis of TIW usage. Its efficacy and safety is reported to be comparable to other alpha IFNs. There is limited data available about daily use of CIFN. A study protocol was designed to investigate efficacy of daily CIFN in patients who have relapsed or not responded to previous IFN alpha 2b treatment. METHODS: Between February and August 1998, a total of 11 (7 male, 4 female) noncirrhotic patients with a mean age of 45.8 ± 9.8 were enrolled into the study. Five were nonresponders and 6 were relapsers. Protocol consisted of daily 15 mcg dose CIFN for the initial 8 weeks followed by daily 9 mcg dose for the following 40 weeks, to complete 1 year of treatment. Serum samples were drawn bi-weekly for the first month and then monthly, for liver function tests and complete blood count. Serum HCV-RNA was tested at the 12th and 48th week of treatment. Treatment failure is described as HCV-RNA positivity at 48th week. RESULTS: All 11 patients completed one year treatment regimen and all were evaluated for virological response. Four patients (44%) needed dose reduction to 9 mcg before the end of the 8th week of treatment because of fatigue and/or leukopenia. Pre-treatment serum HCV-RNA levels of patients were between 20,000 and 1,100,000 copies per mL with a medium of 345,000. As a whole, 8 (72%) patients became serum HCV-RNA negative. Of these, 60% (3/5) were among previous nonresponders and 83% (5/6) were among previous relapsers. HCV-RNA clearance rates were similar at 12th and 48th week. CONCLUSION: Our data suggests that daily use of CIFN provides encouraging results among relapsers and nonresponders. Patients tolerated daily administration of CIFN fairly well with no increase in the incidence of side effects. It is suggested that daily and TIW based treatment options need to be further investigated.

6598

INTERFERON ALPHA THERAPY DECREASES CIRCULATING INTERLEUKIN-18 LEVELS IN HEPATITIS C PATIENTS.

Arthur Kaser, Wolfgang Vogel, Herbert Tilg, Univ Hosp, Dept of Gastroenterology and Hepatology, Innsbruck, Austria.

Interleukin-18 (IL-18) is a newly discovered cytokine derived from macrophages sharing many biological properties with IL-12. Recent reports provide evidence that IL-18 is a major mediator of liver injury in mice. Recently we observed that circulating IL-18 levels in cirrhotic patients are substantially elevated. Therefore we set out to explore the influence of IFN-α as the mainstay of treatment in viral hepatitis, on IL-18 levels in hepatitis C patients. Five female and 9 male patients were treated with high-dose IFN-α (1×10^7 IU) sc and IL-18 levels were assessed at 0, 2, 6, 12, 24, 48, 72 hours, and 7d, 11d, 14d, 17d, 21d, 24d and 28d after institution of therapy. While no significant short-term effects were observed, we noted a progressive decrease in circulating IL-18 levels (113±25pg/ml at 0h vs 53±15pg/ml on day-28, p=0,05). Therefore we suggest that IFN-α might exert its clinically beneficial effects by down-modulating a major pro-inflammatory cytokine. Furthermore our data call into question the notion of IFN-α as a Th1-biasing cytokine.

6599

FULMINANT HEPATIC FAILURE CAUSED BY THE COEXISTENCE OF ACETAMINOPHEN, HEPATITIS C VIRUS AND ALCOHOL.

Vivek Kaul, Angel Fernandez, David Sass, Sandhya Khurana, Rafael E. Pena, Santiago J. Munoz, ALBERT EINSTEIN Med Ctr, Philadelphia, PA; SUNY DOWNSTATE Med Ctr, Brooklyn, NY.

Introduction: Chronic alcoholism is a risk factor for severe acetaminophen (APAP) hepatotoxicity, including cases with intake of APAP within therapeutic range. Given the relatively high frequency of alcoholism (ETOH), chronic hepatitis C virus infection (HCV) and APAP usage, it is important to study the effects of these three offending agents when simultaneously present in a patient. Case: We describe a 62 yr. old African-American woman with a history of chronic ETOH use (approx. 60 g/day for 40 years) admitted with abdominal pain, nausea, vomiting, jaundice and altered mental status after ingesting 1-1.5 g/day of APAP for shoulder pain during the 4 days preceding admission. On physical examination, she had grade III encephalopathy and icterus but no stigmata of chronic liver disease. Initial laboratory data: arterial pH: 7.1; APAP level: 158.9 μg/ml (therapeutic range:10-25 μg/ml); total bilirubin: 4.7 mg/dl (peak value: 32.4 mg/dl); AST: 19,621 U/L; ALT: 4,545 U/L; prothrombin time: 24.3 sec.; creatinine: 5.7 mg/dl; ammonia: 161μmol/L; Factor V: 21% and Factor VII: 17%. Serological profile revealed a positive HCV antibody test (EIA-II) with a viral load of > 1 million (HCV RNA by PCR). The patient satisfied all of the poor prognostic criteria of APAP induced-fulminant hepatic failure identified by King's College criteria and other prognostic methods. N-acetylcysteine administration was begun within 6 hours of presentation. The patient's twelve-day ICU course was complicated by multi-system organ failure (acute renal failure, pancreatitis, ARDS with respiratory failure, intravascular coagulopathy, bacterial peritonitis, sepsis and rhabdomyolysis). However, with aggressive critical care the patient's condition gradually improved, despite a dismal prognosis. She was discharged home three weeks after admission. She remains clinically stable and is followed as an outpatient. She is currently undergoing alcohol rehabilitation in preparation for consideration for HCV antiviral therapy. Conclusion: This patient demonstrates that even when three major causes of liver injury simultaneously co-exist in an individual and induce fulminant hepatic failure meeting the criteria for a worse prognosis, aggressive and persistent intensive medical care may lead to recovery without the need for liver transplantation.